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Canadian Adverse Drug Reaction Newsletter

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Antitubercular drugs (isoniazid, rifampin and pyrazinamide): hepatobiliary reactions

According to the latest edition of the *Canadian Tuberculosis Standards*,[1] Canada has one of the lowest reported incidence rates of tuberculosis (TB) in the world. However, in Canada, the high-risk groups for *Mycobacterium tuberculosis* infection are HIV-positive people, Aboriginals, foreign-born people from countries with a high prevalence of TB, intravenous drug users and homeless people.

The Canadian Lung Association recommends 2 standard drug regimens for the treatment of TB: a combination of isoniazid (INH), rifampin (RI) and pyrazinamide (PY) (with or without ethambutol [EMB]) and a combination of INH and RI (with or without EMB).[1] Of these agents, INH, PY and RI have been associated with liver toxicity. INH and PY are considered to be major hepatotoxins, whereas RI is considered to be relatively less hepatotoxic but is a powerful enzyme inducer, which may enhance the hepatotoxicity of INH.[2] Severe and sometimes fatal hepatitis associated with regimens containing INH, PY and RI has been well documented. Two cases were recently published of liver failure in patients receiving combination therapy with RI and PY for latent TB; one patient died.[3]

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The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) reviewed 420 suspected domestic reports of hepatobiliary adverse reactions associated with different combinations of INH, PY and RI that were received from the time of their introduction in Canada to May 18, 2001. (Each report may have contained more than one of the following reaction terms; however, each report was included only under the most important reaction term):

- INH alone: 258 reports of hepatic reactions (7 deaths).
- PY alone: 4 reports: 2 of hepatitis, and 1 each of hepatic failure and jaundice.
- RI alone: 27 reports: 12 of jaundice, 6 of hepatitis, 5 of abnormal liver enzyme levels, 3 of hepatocellular damage (1 death), and 1 of hepatomegaly.
- INH and PY: 1 report of hepatic failure (1 death).
- INH and RI: 110 reports: 50 of abnormal liver enzyme levels (1 death), 27 of hepatitis (2 deaths), 18 of jaundice (2 deaths), 9 of hepatocellular damage (1 death), 2 each of hepatic failure and hepatomegaly, and 1 each of cholelithiasis and hepatic cirrhosis.
- RI and PY: 1 report of jaundice.
- INH, RI and PY: 19 reports: 7 of abnormal liver enzyme levels, 6 of hepatitis, 4 of jaundice and 1 each of hepatic coma and hepatic necrosis.

These reports suggest that liver toxicity may occur in patients receiving any of the drugs alone or in combination. The *Canadian Tuberculosis Standards* recommends baseline liver function testing when INH is used and regular monitoring only in patients who have pre-existing liver disease or a history of alcohol abuse or who are 35 years of age or older.[1] The usefulness of liver function monitoring to detect fulminant liver failure is a controversial issue and needs to be further investigated. However, health care professionals are reminded that monitoring for liver toxicity (either through liver enzyme measurement or clinical monitoring) is important during treatment with any antitubercular regimen.[2] It is essential to instruct patients to watch for symptoms suggestive of hepatitis (nausea, vomiting, stomach pain, lack of appetite, tiredness, dark urine or yellowing of the skin), and to stop taking their antitubercular medication and to consult their physician immediately if these symptoms occur.[3]

Written by: Duc Vu, PhD, and Lynn Macdonald, BSP, Bureau of Licensed Product Assessment.

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Health Professional Advisories

Health professional advisories are an important source of information on the post-approval safety and effectiveness of therapeutic products. The following is a list of links to recent advisories issued since June 2001 by the Therapeutic Products Directorate and the Biologics and Genetic Therapies Directorate of Health Canada and by industry:

- Aug. 17, 2001: Do not use products labelled to contain Aristolochia
  www.hc-sc.gc.ca/english/archives/warnings/2001/2001_91e.htm
- Aug. 15, 2001: Interaction between warfarin and vaginal miconazole
  www.hc-sc.gc.ca/english/archives/warnings/2001/2001_90e.htm
- Aug. 10, 2001: Voluntary withdrawal of Baycol
  www.hc-sc.gc.ca/english/archives/warnings/2001/2001_89e.htm
- Aug. 8, 2001: Market withdrawal of Baycol (cerivastatin)
  http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/baycol_cerivastatin_e.pdf
- July 16, 2001: Cerivastatin (Baycol) and gemfibrozil — increased risk of rhabdomyolysis — concomitant use contraindicated
  http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/baycol_e.pdf
- July 10, 2001: Clinically important safety labelling change for prescription strength of famotidine: dosage adjustments for patients with moderate and severe renal impairment
  http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/tpd/famotidine_e.pdf
- July 9, 2001: Risk of severe liver injury associated with use of the antidepressant Nefazodone
  www.hc-sc.gc.ca/english/archives/warnings/2001/2001_74e.htm
- July 4, 2001: Important safety information on Amiodarone Intravenous
  http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/amiodarone_e.pdf
- July 3, 2001: Important safety information regarding bupropion (Zyban, Wellbutrin)
  http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/zyban_e.pdf
- June 28, 2001: Important safety information regarding Nefazodone HCl: severe and serious hepatic events
  http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/apo-nefazodone_e.pdf
- June 20, 2001: Important safety information on Nefazodone HCl (from Bristol-Myers Squibb Canada Inc. and Linson Pharma Inc.)
  http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/nefazodone_e.pdf
- June 19, 2001: Hydroview IOL lens product (from Bausch & Lomb Canada Inc.)
  http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/hydroview_iol_e.pdf
- June 14, 2001: Advisory not to use products containing Ephedra or ephedrine
  http://www.hc-sc.gc.ca/english/archives/warnings/2001/2001_67e.htm
- June 2001: Drug products containing phenylpropanolamine: updated list
  http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/tpd/ppa_list_e.pdf

Atypical antipsychotics: impaired glucose metabolism

The new atypical antispychotics clozapine, olanzapine, quetiapine and risperidone are among the first-line treatments for managing psychotic disorders, mainly because they are associated with superior effectiveness in controlling the negative symptoms (blunted affect, emotional and social withdrawal) of schizophrenia.[1] Some atypical antipsychotics have been associated with impaired glucose metabolism.[2] Since 1994, there have been at least 29 published cases of impaired glucose metabolism associated with the use of clozapine and 26 with olanzapine[2,3] (other references are available upon request). Since

February 1999, there have been 2 published cases in which risperidone was associated with diabetic ketoacidosis or elevated blood glucose levels,[4,5] and 2 published cases of new-onset diabetes mellitus with quetiapine.[2,6] In 1999, the results of a cross-sectional study revealed a possible association between type 2 diabetes and antipsychotics.[7] Specifically, diabetes was diagnosed in 15.5% of schizophrenic patients treated with clozapine, 11% of those treated with olanzapine and 6% of those treated with risperidone.[7]

Clozapine, olanzapine, quetiapine and risperidone were introduced in Canada in 1991, 1996, 1997 and 1993 respectively. By June 7, 2001, a total of 37 domestic case reports of suspected impaired glucose metabolism associated with these drugs were reported to the Canadian Adverse Drug Reaction Monitoring Program. Patient characteristics and important adverse reactions are summarized in Tables 1 and 2 respectively.

In 17 of the 37 cases, the reactions occurred within 5 months of treatment onset. Similarly, in published cases, impaired glucose metabolism associated with atypical antipsychotics often occurred relatively soon following the start of treatment (i.e., in as little as 10 days with clozapine, 15 days with olanzapine and 1 month with quetiapine).[2] Of the 35 reports in which disorders of hyperglycemia were denoted, there were 4 cases of pre-existing diabetes; 24 cases were considered to be new onset on the basis of the evidence in the report, with 14 clearly noted as being new-onset diabetes mellitus. One of the cases occurred 2 weeks after discontinuation of risperidone therapy and involved an intentional overdose. There were 2 reports of hypoglycemia; both patients had a prior history of diabetes before this reaction.

Of the 10 cases in which "diabetic ketoacidosis" or "ketoacidosis" was reported (Table 2), the possibility of alcohol consumption or substance use was noted in 4 cases, and abnormal liver function test results were reported in 2 cases. Three of these 10 patients died.

Schizophrenic patients may be predisposed to diabetes mellitus and associated disorders due to factors such as reduced physical activity, poor diet and co-existing illnesses.[8] In addition, the involvement of concomitant medications such as divalproex sodium,[9,10] lithium[10] and other drugs metabolized by the liver[11,12] cannot be ruled out as contributing to the abnormal glucose metabolism associated with clozapine[12,13] or olanzapine.[10,11] Other risk factors for hyperglycemia or ketoacidosis in patients taking clozapine or olanzapine may include being male, non-White and age of about 40 years.[14]

Obesity is another major risk factor for diabetes.[14] Among the Canadian reports, there was a case of a 33-year-old man who took olanzapine (15 mg/d) and gained between 22 and 45 kg over 1 year after starting olanzapine therapy. It was reported that diabetes developed as a result of this weight gain.

It has been speculated that multiple receptor antagonism (dopamine, serotonin, histamine) may be involved in the development of non-insulin-dependent diabetes mellitus associated with atypical antipsychotics.[2] Specifically, antagonism of histaminic and possibly serotonergic receptors may induce weight gain, which in turn, may lead to changes in glucose metabolism, and that these changes may have a causal role in neuroleptic-induced hyperglycemia.[11] Serotonin antagonism may decrease the responsiveness of pancreatic • -cells, which would result in low insulin levels and ensuing hyperglycemia.[11] Diabetes induced by atypical antipsychotics may be attributed to multiple factors, and the mechanism of action remains unclear.[2]

Atypical antipsychotics may be associated with new-onset diabetes mellitus and diabetic ketoacidosis. Patients may require glucose monitoring upon initiation and titration of antipsychotic medications, and regular monitoring thereafter.[15,16]

Written by: Jenna Griffiths, MSc, PhD, and Pascale Springuel, BPharm, Bureau of Licensed Product Assessment.

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Table 1: Characteristics of patients with impaired glucose metabolism associated with atypical antipsychotics reported to the CADRMP as of June 7, 2001*

Characteristic	Clozapine *n* = 17†	Olanzapine *n* = 10‡	Quetiapine *n* = 3§	Risperidone *n* = 7
Mean age (and range), yr	45 (26–74)	34 (26–46)	30 (30)¶	48 (11–78)
Female:male ratio	6:10**	4:6	0:2**	6:1
Period of onset of impaired glucose metabolism	18 d to 6.5 yr	11 d to 5 yr	2.5 to 4 mo	2 d to 8 mo††
Daily dose of atypical antipsychotic	100 to 775 mg	7.5 to 30 mg	300 to 700 mg	1 to 6 mg††
Maximum recommended daily dose	900 mg	20 mg	750 mg	6 mg

Note: CADRMP = Canadian Adverse Drug Reaction Monitoring Program.

***These data cannot be used to determine the incidence of ADRs because neither the prescribing rate nor the amount of time the drug was on the market has been taken into consideration. Also, see caveat at the end of the newsletter.**

†Concomitant medication was risperidone (6 mg/d) in 1 case.

‡Clozapine and olanzapine were reported as co-suspect medications in 1 case report, but from the evidence provided, olanzapine was considered the suspect drug.

§Quetiapine and risperidone were reported as co-suspect medications in 1 case report, but from the evidence provided, quetiapine was considered the suspect drug.

¶Age not specified in 1 case.

**Sex not specified in 1 case.

††Case of overdose not included.

Table 2: Glucose-related reaction terms reported in the Canadian case reports associated with clozapine, olanzapine, quetiapine, risperidone

Reaction term *	Drug; no. of reports			
	Clozapine	Olanzapine	Quetiapine	Risperidone
Coma diabetic	–	2	–	–
Diabetes mellitus	8	2	1	1
Diabetic ketoacidosis/ ketoacidosis†	5‡	3	2	–
Hyperglycemia	4	3	–	3
Hypoglycemia	–	–	–	2
Labile blood sugar†	–	–	–	1

*Based on the "preferred term" of the World Health Organization (WHO) Adverse Reaction Dictionary (WHOART). Each report may contain more than 1 of these reaction terms, however, reports were only included in the most significant category.

†Terminology other than WHO "preferred term" was used.

‡One case also involved "coma diabetic."

COMMUNIQUÉ

The CADRMP wishes to provide feedback and increase awareness of recently reported ADRs. The following cases have been selected on the basis of their seriousness, or the fact that the reactions do not appear in the official Canadian product monograph. (Reactions are expressed based on the "preferred term" in the World Health Organization *Adverse Reaction Dictionary*.)

Brimonidine (Alphagan) ophthalmic drops: accidental ingestion

Accidental oral ingestion of brimonidine ophthalmic drops (about 2 mL) in a 28-month-old child caused decreased consciousness and apnea resulting in intubation, ventilation and surveillance in an intensive care unit for 40 hours. Recommendations for child-resistant packaging were made to the manufacturer. As an immediate option to reduce the risk of accidental exposure, consider dispensing these ophthalmic drops in childproof vials.

If you have observed any suspected ADRs with the drug in the Communiqué, *please report them* to the :

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Adverse Reaction Information Unit
Bureau of Licensed Product Assessment
AL: 0201C2, Ottawa, ON K1A 1B9
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Consumers and Health Professionals may contact us Toll free at:
Tel: 866 234-2345, Fax: 866 678-6789
Email: cadrmp@hc-sc.gc.ca

The ADR form is available from the *Compendium of Pharmaceuticals and Specialties* and the National and Regional ADR Centres, and at:

http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf
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Health Professionals and Consumers may report Adverse Drug Reactions toll-free:

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Please Note: A voluntary reporting system thrives on intuition, lateral thinking and open mindedness. Most adverse drug reactions (ADRs) can only be considered to be suspicions, for which a proven causal association has not been established. Because ADRs are under reported and because a definite causal association cannot be determined, spontaneous ADR reports cannot be used to estimate the incidence of adverse reactions. ADRs are nevertheless valuable as a source of potential new and undocumented signals. Health Canada does not assume liability for the accuracy or authenticity of the ADR information contained in the newsletter articles. Furthermore, the Therapeutic Products Directorate monitors and assesses suspected ADRs as a means of continuously evaluating drug safety profiles. Regulatory decisions are not made within the context of this newsletter.

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